

09/871.610

-5-

surface has a surface upon which said nucleic acid array is prepared. Support for the amendment can be found, for example, at page 4, line 29 to page 5, line 2 of the specification.

Claim 1 has also been amended to consistently use the term "support", rather than a combination of "support" and "substrate",

Claim 1 has further been amended to recite that the surface of the support is maintained in a vertical position or within about 30 degrees of vertical during at least step (b) or (c), as well as recite that the rotated support has a different position relative to the support in the prior attaching or binding step and that at least one of said attaching or binding steps occurs after said support is rotated. Support for the amendment can be found, for example, at page 17, lines 14 to 27, page 20, lines 1 to 8, and Figure 1.

Claims 2 to 5 have been amended to replace the phrase "said rotating is conducted" or "said rotating" with "said support is rotated" for consistency of language.

Claims 6 and 7 have been amended to replace the term "interface" with "surface of said support", which finds proper antecedent basis in Claim 1. Claims 6 and 7 have also been amended to replace the phrase "said rotating" with "said support is rotated" for consistency of language.

Claim 7 has been amended to explicitly recite that the square planar silica chip has four vertices, which is an inherent characteristic of all squares.

Claim 8 has been amended to correct a typographical error.

Claims 9 to 13 have been amended to replace "formed" with "synthesized". Support for the amendment can be found in lines 16 to 18 of Claim 1. Claims 9 to 13 have also been amended to replace the phrase "different nucleic acids" with "nucleic acids" and a clause reciting that each of the specified nucleic acids is different from each of the other specified nucleic acids, in order to provide consistency of language.

Claims 14 and 15 have been amended to recite that each separate known region has an area of less than about 1 cm<sup>2</sup> or less than about 1 mm<sup>2</sup>.

#### Objection to Claim 8

Claim 8 is objected to because "vertices" is misspelled. The claim has been amended to correct the spelling. Withdrawal of the objection is respectfully requested.

09/871.610

-6-

Rejection of Claims 1-15 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claimed the subject matter which Applicants regard as the invention. Applicants will respond to the rejection according to the subheadings used by the Examiner.

A. The Examiner states Claim 1-15 are indefinite because Claim 1 is drawn to a method of preparing a nucleic acid array on a support, but the claim does not recite method steps of array preparation and does not result in a nucleic acid array on a support.

The specification defines an "array" at page 4, lines 5 to 11, as an intentionally created collection of nucleic acids which can be prepared either synthetically or biosynthetically. A "nucleic acid" is defined at page 4, lines 11 to 28, of the specification as a polymeric form of nucleotides of any length.

The method steps of Claim 1 clearly result in the preparation of a collection of nucleic acids attached to a support. Thus, a nucleic acid array is prepared on the support. Claim 1 has been amended in step (f) to recite that a nucleic acid array is prepared as a result of the method steps.

B. The Examiner states Claims 1-15 are indefinite because the recitation of "the surface of said substrate" in Claim 1 lacks proper antecedent basis.

Claim 1 has been amended to recite in the preamble that the support has a surface upon which said nucleic acid array is prepared, which provides proper antecedent basis for "the surface of said support."

C. The Examiner states that Claims 6 and 7 are indefinite because the recitation "said interface" lacks proper antecedent basis in Claim 1.

Claims 6 and 7 have been amended to replace "interface" with "surface of said support", which finds proper antecedent basis in Claim 1.

09/871,610

-7-

D. The Examiner states that Claim 8 is indefinite because the recitation "one of the four square vertices" lacks proper antecedent basis in Claim 7.

Claim 7 has been amended to explicitly recite that the square planar silica wafer has four vertices, which is an inherent property of any square object.

E. The Examiner states that Claims 9-13 are indefinite because the recitation "formed" lacks proper antecedent basis in Claim 1.

Claims 9-13 have been amended to replace "formed" with "synthesized", which is recited in Claim 1 and provides proper antecedent basis for Claims 9-13.

F. The Examiner states that Claims 14 and 15 are indefinite because the recitation "each different nucleic acid" lacks proper antecedent basis in Claim 1.

Claims 14 and 15 have been amended to recite that "each separate known region of the support" has an area of less than about 1 cm<sup>2</sup> or less than about 1 mm<sup>2</sup>, for which proper antecedent basis can be found in Claim 1.

Applicants have thus addressed all aspects of the rejection made under 35 U.S.C. § 112, second paragraph. Applicants submit that the claims, as amended, even more distinctly point out and distinctly claim the subject matter which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-6, 14 and 15 Under 35 U.S.C. § 102(e)

Claims 1-6, 14 and 15 are rejected under 35 U.S.C. § 102(e) as being anticipated by Gamble, *et al.* (U.S. Patent No. 5,981,733; Reference A). The Examiner states that Gamble, *et al.*, disclose a method of preparing a nucleic acid array on a support encompassing all of the recitations of Claim 1.

Gamble, *et al.* disclose an apparatus for the automated synthesis of molecular arrays on a substrate. The apparatus includes a jetting device, a reaction chamber to dispense reagents used in the synthesis onto the substrate and optionally a wash station. A positioning system is used to move the substrate among the jetting device, the reaction chamber and the wash station. The

09/871,610

-8-

positioning system can be capable of rotating the substrate parallel and/or perpendicular to the surface of the substrate.

Gamble, *et al.*, however, do not disclose that the substrate is rotated such that the rotated substrate has a different position relative to the support in the prior attaching or binding step. Although Gamble, *et al.* may rotate the substrate between attaching or binding steps to facilitate movement among the jetting device, reaction chamber and wash station, there is no disclosure that the support is positioned differently in sequential attaching or binding steps. The claimed invention recites, *inter alia*, that the support is rotated around an axis perpendicular to the surface by an amount of from about 20 degrees to about 180 degrees, with the rotating being done prior to, coincident with or subsequent to at least one of the attaching or binding steps, **whereby the rotated support has a different position relative to the support in the prior attaching or binding step.** See Figure 1 of the subject application for a representation of different positions. Thus, Gamble, *et al.* do not teach or suggest all of the recitations of Claim 1, as amended. Reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 7 and 8 Under 35 U.S.C. § 103(a)

Claims 7 and 8 are rejected under 35 U.S.C. § 103(a) as being obvious over Gamble, *et al.* in view of Bass, *et al.* (U.S. Patent No. 6,440,669; Reference C). The Examiner states that it would have been obvious to apply the square planar silica substrate of Bass, *et al.* to the substrate of Gamble, *et al.* based on its well known use as an array substrate.

As discussed above, Gamble, *et al.* does not disclose that the support is rotated such that it is positioned differently in sequential attaching or binding steps. Bass, *et al.* do not disclose that the position of the support is altered during the attaching or binding steps of preparing a nucleic acid array. Therefore, Bass, *et al.* do not remedy the deficiencies of Gamble, *et al.*, and Claims 7 and 8 are not obvious over Gamble, *et al.* in view of Bass, *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 9-13 Under 35 U.S.C. 103(a)

Claims 9-13 are rejected under 35 U.S.C. § 103(a) as being obvious over Gamble, *et al.* in view of Brennan (U.S. Patent No. 5,985,551; Reference B). The Examiner states that it would

(978) 341-0136

-9-

have been obvious to apply the high density array teaching of Brennan to the array of Gamble, *et al.* and to form at least 10, 100, 1000, 10,000 or 100,000 different nucleic acids on the surface of the support.

As discussed above, Gamble, *et al.* does not disclose that the support is rotated such that it is positioned differently in sequential attaching or binding steps. Brennan does not disclose the position of the support during preparation of a nucleic acid array. Thus, Brennan does not remedy the deficiencies of Gamble, *et al.*, and Claims 9-13 are not obvious over Gamble, *et al.* in view of Brennan. Reconsideration and withdrawal of the rejection are respectfully requested.

#### CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Jesse A. Pecker

Jesse A. Pecker

Registration No. P52,883

Telephone: (978) 341-0036

Facsimile: (978) 341-0136

Concord, MA 01742-9133

Dated:

June 3, 2003

09/871,610

-i-

MARKED UP VERSION OF AMENDMENTSClaim Amendments Under 37 C.F.R. § 1.121(e)(1)(ii)

1. (Amended) A method of preparing a nucleic acid array on a support having a surface upon which said nucleic acid array is prepared, wherein each nucleic acid occupies a separate known region of the support, said synthesizing comprising:
- (a) activating a region of the support;
  - (b) attaching a nucleotide to a first region, said nucleotide having a masked reactive site linked to a protecting group;
  - (c) repeating steps (a) and (b) on other regions of said support whereby each of said other regions has bound thereto another nucleotide comprising a masked reactive site linked [link] to a protecting group, wherein said another nucleotide may be the same or different from that used in step (b);
  - (d) removing the protecting group from one of the nucleotides bound to one of the regions of the support to provide a region bearing a nucleotide having an unmasked reactive site;
  - (e) binding an additional nucleotide to the nucleotide with an unmasked reactive site;
  - (f) repeating steps (d) and (e) on regions of the support until a desired plurality of nucleic acids is synthesized, each nucleic acid occupying a separate known region [regions] of the support, thereby preparing a nucleic acid array on said support;
- wherein the surface of said support [substrate] is maintained in a position which is vertical or within 30 degrees of vertical during at least step (b) or (e), [and]
- wherein the support [substrate] is rotated around an axis perpendicular to said surface by an amount of from about 20 degrees to about 180 degrees, said rotating being done prior to, coincident with or subsequent to at least one of said attaching or binding steps, whereby said rotated support has a different position relative to the support in the prior attaching or binding step, and
- wherein at least one of said attaching or binding steps occurs after said support is rotated.

09/871,610

-ii-

2. (Amended) A method in accordance with claim 1, wherein said support is rotated [rotating is conducted] prior to, coincident with or subsequent to at least 50% of said attaching or binding steps.
3. (Amended) A method in accordance with claim 1, wherein said support is rotated [rotating is conducted] prior to, coincident with or subsequent to at least 80% of said attaching or binding steps.
4. (Amended) A method in accordance with claim 1, wherein said support is rotated [rotating is] in an amount of from about 75 to about 105 degrees.
5. (Amended) A method in accordance with claim 1, wherein said support is rotated [rotating is] in an amount of about 90 degrees.
6. (Amended) A method in accordance with claim 1, wherein said surface of said support [interface] is vertical or within about 10 degrees of vertical and said support is rotated [rotating is] in an amount of about 90 degrees.
7. (Amended) A method in accordance with claim 1, wherein said substrate is a substantially square planar silica chip having four vertices, said surface of said support [interface] is vertical or within about 10 degrees of vertical and said support is rotated [rotating is] in an amount of about 90 degrees.
8. (Amended) A method in accordance with claim 7, wherein said substantially square planar silica chip is held in a vertical position with one of the four [square] vertices [verticies] pointing downward.
9. (Amended) A method in accordance with claim 1, wherein at least 10 [different] nucleic acids are synthesized [formed] on said surface and wherein each of said 10 nucleic acids is different from each other of said 10 nucleic acids.

02/871.610

-iii-

10. (Amended) A method in accordance with claim 1, wherein at least 100 [different] nucleic acids are synthesized [formed] on said surface and wherein each of said 100 nucleic acids is different from each other of said 100 nucleic acids.
11. (Amended) A method in accordance with claim 1, wherein at least 1000 [different] nucleic acids are synthesized [formed] on said surface and wherein each of said 1000 nucleic acids is different from each other of said 1000 nucleic acids.
12. (Amended) A method in accordance with claim 1, wherein at least 10,000 [different] nucleic acids are synthesized [formed] on said surface and wherein each of said 10,000 nucleic acids is different from each other of said 10,000 nucleic acids.
13. (Amended) A method in accordance with claim 1, wherein at least 100,000 [different] nucleic acids are synthesized [formed] on said surface and wherein each of said 100,000 nucleic acids is different from each other of said 100,000 nucleic acids.
14. (Amended) A method in accordance with claim 1, wherein each separate known [different] nucleic acid is in a] region of the support has an area of less than about 1 cm<sup>2</sup>.
15. (Amended) A method in accordance with claim 1, wherein each separate known [different] nucleic acid is in a] region of the support has an area of less than about 1 mm<sup>2</sup>.